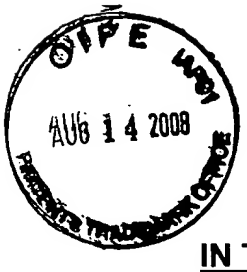

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/972,916	Confirmation No.: 4645
Applicant	:	Peter M. THULÉ, M.D.	
Filed	:	October 10, 2001	
Title	:	GLUCOSE SENSITIVE REGULATOR OF INSULIN TRANSCRIPTION	
Group Art Unit	:	1635	
Examiner	:	ANGELL, Jon E.	
Atty. Docket No.	:	US 1292/01(VA)	
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APPEAL BRIEF

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C. Vaulont et al., *J. Mol. Biol.*, Vol. 209, pp. 205-219 (1989).

D. Goswami et al., *Endocrinology*, Vol. 134, pp. 736-743 (1994).

E. Unterman TG, Lacson RG, McGary E, Whalen C, Purple C, Goswami RG. Cloning of the rat insulin-like growth factor binding protein-1 gene and analysis of its 5' promoter region. *Biochemical Biophysical Research Communication*, 185(3):993-999 (1992).

F. Unterman TG, Fareeduddin A, Harris MA, Goswami RG, Porcella A, Costa RH, et al. Hepatocyte nuclear factor-3 (HNF-3) binds to the insulin response sequence in the IGF binding protein-1 (IGFBP-1) promoter and enhances promoter function. *Biochemical Biophysical Research Communication*, 203:1835-1841 (1994).

G. Cognet M, Lone YC, Vaulont S, Kahn A, Marie J. Structure of the rat L-type pyruvate kinase gene. J Mol Biol, 196:11-25 (1987).

H. Inoue H, Noguchi T, Tanaka T. Complete amino acid sequence of rat L-type pyruvate kinase deduced from the cDNA sequence. *European Journal of Biochemistry*, 154(2):465-9 (1986).

I. Yamada K, Tanaka T, Noguchi T. Members of the nuclear factor 1 family and hepatocyte nuclear factor 4 bind to overlapping sequences of the L-11 element of the rat pyruvate kinase L gene promoter and regulate its expression. *Biochem J.*, 324:917-925 (1997).

J. Genes & Genomes (Sanger and Burg, 1991).

CLAIMS APPENDIX

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the U.S. Department of Veterans Affairs, the assignee of record.

II. RELATED APPEALS AND INTERFERENCES

There are no prior and pending appeals, judicial proceedings or interferences known to the Appellant which may be related to, directly affect, or be directly affected by, or have a bearing on the Board's decision in the present appeal.

III. STATUS OF CLAIMS

Claims 1-21 were filed with the application on October 10, 2001. Claims 1-15 stand rejected. Claim 16 has been cancelled. Claims 17-21 are withdrawn.[1] Accordingly, Claims 1-15 are presented herein on appeal.

IV. STATUS OF AMENDMENTS

No Amendment under 37 CFR §1.116 was filed responsive to the Office Action (Final Rejection) of December 12, 2007.

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[1] It is noted that withdrawn Claims 17-21 are process claims that depend from or otherwise include all the limitations of the allowable independent product Claim 9. Although these claims are not before the Board, Appellant requests rejoinder under MPEP §821.04, upon allowance of the product Claims 1-15.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The sole independent Claim 9 recites an insulin regulator construct that includes a nucleotide sequence set forth in one of SEQ ID NOs: 3-6, and a sequence encoding insulin or proinsulin operably linked to the promoter element of the construct. See the Sequence Listing filed with the PTO on April 21, 2004.[2] Also see Figures 1A-1B and Page 7, lines 5-21 of the specification. The nucleotide sequence includes one or more glucose response elements (GIREs) of rat liver pyruvate (L-PK) gene promoter and an insulin-sensitive element of an insulin-like growth factor binding protein-1 (IGFBP-1) basal promoter. Therefore, the claimed construct includes at least one glucose response element (GIRE), an insulin-sensitive element, and a sequence encoding insulin or proinsulin (2xfur).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 1-15 are unpatentable under 35 U.S.C. § 102(b) over Thulé et al. (Diabetes, May 1999, supplement) as evidenced by Thulé and Liu presentation at the ADA 59th Annual Meeting, June 1999 (Reference #3 in the IDS filed on March 14, 2006), and Vaulont et al. (*J. Mol. Biol.* 1989, Vol. 209, pp. 205-219) and Goswami et al. (*Endocrinology*, 1994, Vol. 134, pp. 736-743) publications.

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[2] It is noted herewith that in response to the election of species requirement set forth in the Office Action of February 25, 2004, the Applicant elected, with traverse, the species set forth in SEQ ID NO: 5. The sole independent Claim 9 is generic to the species of SEQ ID NOs: 3-6.

2. Whether Claims 1-15 are unpatentable under 35 U.S.C. § 102(b) over Thulé et al. (Abstract from Meeting June 9-13, 1999) as evidenced by Thulé and Liu presentation at the American Society of Gene Therapy, 2nd Annual Meeting (Reference #4 in the IDS filed on March 14, 2006), June 1999, and Vaulont et al. (*J. Mol. Biol.* 1989, Vol. 209, pp. 205-219) and Goswami et al. (*Endocrinology*, 1994, Vol. 134, pp. 736-743) publications.

3. Whether Claims 1-15 are unpatentable under 35 U.S.C. § 102(b) over Thulé et al. (Abstract from Meeting of June 1998) as evidenced by Thulé and Liu presentation at the ADA 58th Annual Meeting, June 1998 (Reference #2 in the IDS filed on March 14, 2006), and Vaulont et al. (*J. Mol. Biol.* 1989, Vol. 209, pp. 205-219) and Goswami et al. (*Endocrinology*, 1994, Vol. 134, pp. 736-743) publications.

VII. ARGUMENT

A. REJECTIONS UNDER 35 U.S.C. §§ 101, 103 AND 112

The only rejections set forth by the Examiner in the Final Rejection of December 12, 2007, are based on 35 U.S.C. § 102(b). Therefore, it is respectfully submitted that there are no issues under 35 U.S.C. §§ 101, 103 and 112. The only remaining issues are, therefore, whether the appealed Claims 1-15 are anticipated by the prior art.

B. REJECTIONS UNDER 35 U.S.C. § 102(b) OVER THULÉ et al. ABSTRACTS, THULÉ AND LIU PRESENTATIONS, AND VAULONT et al. AND GOSWAMI et al.

In support of his three separate rejections of Claims 1-15 under 35 U.S.C. §102(b), over three individual Thulé et al. Abstracts, and three individual Thulé and Liu presentations, supplemented by Vaulont et al. and Goswami et al. publications, the Examiner advanced the same arguments. Therefore, for brevity and economy, and to enable the Board to more quickly follow the Appellant's arguments, only one set of arguments is provided below that applies equally to all three rejections, unless specifically noted.

It would be enormously useful, at this point, to summarize the nature of the Examiner's three rejections of Claims 1-15 under 35 U.S.C. §102(b). Each rejection was formulated "as being anticipated" by a Thulé et al. Abstract, with the term "as evidenced by" a Thulé and Liu presentation, and Vaulont et al. and Goswami et al. publications. Therefore, the Examiner relied on the Abstracts, the presentations given by the Applicant, and Vaulont et al. and Goswami et al. publications.[3]

[3] In a personal interview on September 14, 2007, the Examiner clarified that the term "as evidenced by" used in formulating his three rejections means that the Abstracts (used as primary references) are the same as the corresponding Thulé and Liu presentations, and acknowledged that Thulé Abstracts do not explicitly disclose the sequences of Claim 9.

Claim 9

a. The Anticipation Rejections Each Fails the Requirements of 35 U.S.C. §102(b)

Section 102 of Title 35 of the United States Code provides, in pertinent part, as follows:

Section 102 - **Conditions for patentability; Novelty and Loss of Right to Patent**

> A person shall be entitled to a patent unless-
> b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

In accordance with the statute, a person is entitled to a patent, unless one of the specified conditions (exceptions) is met. In the present situation, the applicable condition is whether or not the invention was described in a printed publication.

It is hornbook law that anticipation under 35 U.S.C. §102(b) must be found in a single reference, device, or process. *Studiengesellschaft Kohle v. Dart Indus Inc.*, 726 F. 2d 724, 220 USPQ 841, 842 (Fed. Cir. 1984). Further, anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983) (citing *Soundscriber Corp. v. United States*, 360 F.2d 954, 960, 148 USPQ 298, 301 (Ct. Cl.), *adopted*, 149 USPQ 640 (Ct. Cl. 1966), *cert., denied*, 469 U.S. 851 (1984). *See also Carella v. Starlight Archery*, 804 F.2d 135, 138, 231 USPQ 644, 646 (Fed. Cir.), *modified on reh'g*, 1 USPQ2d 1209 (Fed. Cir.

1986); *RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 1444, 221 USPQ 385, 388 (Fed. Cir. 1984). In addition, the single prior art reference must disclose each element of the claimed invention "arranged as in the claim." *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984) (citing *Connell v. Sears, Roebuck & Co.*, 772 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983). In other words, even if the single prior art reference includes all the claimed elements, if the arrangement of the elements is different from the prior art arrangement, anticipation will not be present.

It is also well-settled law that prior art under 35 U.S.C. §102(b) must specifically describe the claimed invention to have placed the public in possession of it. *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). In other words, "even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Id.* at 533. The Federal Circuit noted that "[t]his rule is based on 'described in a printed publication' language in 35 U.S.C. §102(b)." *Id.* (emphasis added) (citations omitted). Thus, the law requires description or enabling disclosure in a single prior art reference of each element of the claimed invention as arranged in the claim.

In the present case, the Examiner has relied on not a single reference, but multiple references: Thulé Abstracts, Thulé and Liu presentations, and Vaulont and Goswami publications. Further, the Examiner acknowledged that the Thulé Abstracts (primary references) do not explicitly disclose the sequences of Claim 9

(see Office Action dated March 20, 2007, "Response to Arguments", page 9, 4th ¶, and the Interview Summary attached to the Final Rejection of December 12, 2007).

As noted above, in the personal interview on September 14, 2007, Examiner Angell clarified that his use of the term "as evidenced by" means that the three Thulé Abstracts are the same as the three Thulé and Liu presentations. It is, therefore, clear that the sequences recited in Claim 9 are neither disclosed in the three Thulé Abstracts, nor the three Thulé and Liu presentations. It is further noted, without admission, that Vaulont et al. and Goswami et al. publications arguably appear to disclose elements that merely overlap with the individual elements of the present invention.

Further, in support of his rejections, the Examiner borrows the teaching of the claimed vector from the similarly-named vector in the Thulé Abstracts, adds the nucleotide numbering from the Thulé and Liu presentations, and supplies portions of promoter elements, corresponding to the same numbering as in the presentations, from Vaulont et al. and Goswami et al. publications (see Office Action dated March 20, 2007). Therefore, it is clear that the Examiner has relied on the Thulé Abstracts, the Thulé and Liu presentations, and Vaulont et al. and Goswami et al. publications to combine them to conclude that these provide "an enabling disclosure which teaches the claimed invention." See, for example, page 4, 1st ¶ (full), of the Office Action dated March 20, 2007. Based on these documents and the presentations, the Examiner concluded that the claimed

invention was described in a printed publication[4] in this country more than one year prior to the date of application for patent in the United States.

From the above, one can readily conclude that the Examiner has relied on multiple references, that the Thulé Abstracts, Thulé and Liu presentations, and Vaulont et al. and Goswami et al. publications, completely lack in description of the Claim 9 sequences and are, therefore, non-enabling references. Therefore, none of the three anticipation rejections meets the statutory requirement set forth in 35 U.S.C. §102(b).

b. Thulé and Liu Presentations Do Not Qualify As "printed publications" Under 35 U.S.C. §102(b)

As noted above, the Examiner indicated his use of the term "as evidenced by" in formulating his rejections, to mean that the Thulé Abstracts are the same as the corresponding Thulé and Liu presentations. As also noted above, the Examiner admitted that the Thulé Abstracts do not explicitly disclose the sequences of Claim 9. Therefore, it is logical to conclude from the Examiner's own admission that neither the Thulé Abstracts, nor the Thulé and Liu presentations disclose the sequences of Claim 9.

[4] As provided below, Thulé and Liu presentations do not qualify as printed publications.

Further, as the Examiner stated, since the disclosures of the three Thulé Abstracts are the same as the three Thulé and Liu presentations, it is respectfully submitted that the Thulé and Liu presentations are superfluous and do not add to the deficiencies of the three Thulé Abstracts. Moreover, even if one were to conclude that the Thulé and Liu presentations are not the same as Thulé Abstracts, it is respectfully submitted that the presentations do not qualify as "printed publications" for the purposes of 35 U.S.C. §102(b).

The Federal Circuit in *In re Klopfenstein* affirmed that a presentation that includes a transient display of slides is not necessarily a printed publication. 380 F.3d 1345, 1349 & n.4 72 U.S.P.Q.2d 1117, 1120m4 (Fed. Cir. 2004). The court noted:

> While *Howmedica* is not binding on this court, it stands for the important proposition that the mere presentation of slides accompanying an oral presentation at a professional conference is not per se a "printed publication" for the purposes of §102(b) (emphasis added).

The court noted the "duration" of the display to be an important factor in determining whether or not a temporarily displayed reference is a "printed publication" under 35 U.S.C. §102(b). The more transient the display, the less likely it is to be considered a "printed publication." *In re Klopfenstein*, 380 F.3d 1350.

In view of *Klopfenstein*, the Examiner's assertion that the presentations "were not 'entirely oral,' as slides... were shown." is inapposite (Final Rejection, December 12, 2007, Page 7, 2nd ¶ (full)).

It is respectfully submitted that each of the presentations relied on by the Examiner, was for a very short duration, i.e., about ten minutes, and included PowerPoint presentations of 17, 24, and 30 slides, compared with approximately three days in *In re Klopfenstein*. Copies of the slides were not distributed or later indexed in any database, catalog or library. In other words, each presentation was of a highly transient nature and the slides were not disseminated or otherwise made available. Additionally, the slides did not disclose the sequences of Claim 9. Therefore, the projection of the slides for a limited duration could not disclose the presently claimed invention to the extent necessary to enable a person of ordinary skill in the art to make or use the invention. *Regents of the Univ. of Cal. v. Howmedica Inc.*, 530 F.Supp. 846, 860 (D.N.J. 1981), *aff'd*, 676 F.2d 687 (3d Cir. 1982). Further, the information displayed in the presentations was of a highly complex nature requiring familiarity and high degree of expertise to understand, retain and capture the relevance adequate enough for later reproduction. Therefore, it is respectfully submitted that none of the three presentations relied on by the Examiner qualifies as printed publication for the purposes of 35 U.S.C. §102(b).

c. Examiner's Reliance on Multiple References to Support Anticipation Rejections Under 35 U.S.C. 102(b) Does Not Comport With Modest Flexibility in the "anticipation" Rule

Although under an anticipation rejection, the references cannot be combined,

additional references may be used to interpret the allegedly anticipating reference and shed light on what it would have meant to those skilled in the art at the time the invention was made. *Studiengesellchaft, supra*, 726 F.2d 724, 726-727, 220 USPQ 841, 842 (Fed. Cir. 1984). Further, "extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of the reference." *In re Baxter Travenol Labs.*, 952 F.2d 388, 390, 21 USPQ 2d 1281, 1284 (Fed. Cir. 1991) (emphasis added). However, "such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, v. Monsanto Co.*, 948 F2d 1264, 1268, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). The Federal Circuit in *Continental Can* explained:

> This modest flexibility in the rule that "anticipation" requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges. It is not, however, a substitute for determination of patentability in terms of §103.

948 F.2d 1269.

In summary, although the modest flexibility in the anticipation rule allows consideration of other references, the role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill gaps in the reference. *Scripps Clinic Res. Found v.*

Genentech Inc., 927 F.2d 1565, 1576, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991).

The Federal Circuit stated -

> It is sometimes appropriate to consider extrinsic evidence to explain the disclosure of a reference. Such factual elaboration is necessarily of limited scope and probative value, for a finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill gaps in the reference. *See Studiengesellschaft Kohle, mbH v. Dart Industries, Inc.*, 726 F.2d 724, 727, 220 USPQ 841, 842 (Fed, Cir. 1984) (although additional references may serve to reveal what a reference would have meant to a person of ordinary skill, it is error to build "anticipation" on a combination of these references). If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not §102 anticipation, but §103 obviousness. (Emphasis added).

In another case, the Federal Circuit further noted -

> Although this disclosure requirement presupposes the knowledge of one in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there.

Motorola Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 43 USPQ 2d 1481, 1490 (Fed. Cir. 1997).

Thus, the Federal Circuit has strongly made it clear that "anticipation does not permit an additional reference to supply a missing claim limitation." *Teleflex Inc. v. Ficosa North Am. Corp.*, 299 F.3d 1313, 1335, 63 USPQ 2d 1374, 1388 (Fed. Cir. 2002).

From the applicable case law, it is clear that for the purposes of anticipation, extrinsic evidence may be considered when used to explain, but not expand the meaning of a reference or to fill gaps therein. In the present instance, the Thulé Abstracts (primary references) disclose, at most, a vector Ad/$(GIRE)_3$BP-1 2xfur, without disclosing the specific sequences, as recited in Claim 9. In order to fill this gap of the specifically claimed sequences, the Examiner cited Thulé and Liu presentations, which disclose nucleotide numbering for promoter elements to construct a vector. However, the presentations do not disclose the sequences, as recited in Claim 9. In order again to fill this deficiency or gap in the presentations, the Examiner cited Vaulont et al. and Goswami et al. publications, which, at most, disclose footprints or fragments of promoters containing nucleotide numbering corresponding to the numerical values disclosed in the presentations. In other words, neither Vaulont et al. nor Goswami et al. disclose the precise sequences of Claim 9. From the foregoing, it is clear that the Examiner used the Thulé and Liu presentations to fill in the gap of promoter element numbering missing from the Abstracts, and further used Vaulont et al. and Goswami et al. publications to fill in the gap of sequences missing from the presentations.

In the Final Rejection, dated December 12, 2007, the Examiner cited *In re Baxter Travenol Labs* and supported his reliance on more than one reference "to explain the meaning of the term Ad/(GIRE)$_3$BP-1 2Xfur or any other sequence element." (see Page 6, 1st ¶ (full)). However, in *Baxter Travenol Labs*, the Federal Circuit relied on extrinsic evidence (depositions, declarations and admissions), to explain the meaning of a phrase used in the cited prior art document.

In the present instance, however, the Examiner is using the Thulé and Liu presentations, and Vaulont et al. and Goswami et al. publications, not to explain the meaning of the vector noted in Thulé Abstracts, but rather expand the meaning of the individual elements of the vector itself. The Thulé Abstracts already disclose not only the vector, but also the meaning of the individual promoter elements. For instance, the Thulé Abstract from the ADA 59th Meeting of June 1999, states:

> An insulin transgene was constructed by coupling a glucose - and insulin - sensitive promoter to an insulin expression sequence that enables non-β-cells to secrete mature human insulin. This transgene was then incorporated into an adenoviral vector, Ad/(GIRE)$_3$BP-1 2Xfur.

Likewise, the Thulé Abstract from the American Society of Gene Therapy 2nd Annual Meeting of June 9-13, 1999, states:

> By inserting glucose-responsive elements from the L-pyruvate kinase gene into the insulin-like growth factor binding protein-1 basal promoter, and coupling the resultant chimeric regulatory sequence with a human insulin expression cassette, we created an insulin transgene that is expressed in hepatocytes, is stimulated by glucose, and inhibited by insulin.

The remaining third Thulé Abstract from the ADA 58th Annual Meeting of June 1998, does not even disclose the vector and merely talks about creating four promoters, each containing a stimulatory glucose-response element (GIRE), and an inhibitory insulin response region for regulating transgene expression in response to glucose and insulin.

Therefore, the individual elements of the claimed vector are already explained or talked about in the Thulé et al. Abstracts. What is completely missing from the Thulé Abstracts are the precise sequences as recited in Claim 9, and that is exactly the gap that the Examiner has improperly attempted to fill by relying on the Thulé and Liu presentations, and Vaulont et al. and Goswami et al. publications.

More specifically, the Examiner supplies the precise sequence gaps in the Thulé et al. Abstracts by first finding, in the Thulé and Liu presentation, the numerical positions of the nucleotides corresponding to the elements in the vector, and then supplying the nucleotide sequences from Vaulont et al. and Goswami et al. publications, making the supposition that the numerical positions of the nucleotides in the claimed vector are the same as those disclosed in Valount et al. and Goswami et al. publications. In other words, the Examiner reconstructs the claimed invention by mechanically combining individual elements from the Thulé Abstracts, Thulé and Liu presentations, and Vaulont et al. and Goswami et al. publications.

It is respectfully submitted that the numbers presented in the Thulé and Liu presentation slides are ambiguous, and non-enabling to one skilled in the art. It is noted that the numbers referring to bases or base pairs in genetic sequence data are only interpretable when combined with a referenced origin. An origin or referenced start of numbering was not provided in the presentations. The sequence numbers provided are, therefore, non-specific and ambiguous.

In this regard, it is noted that the inventor has been unable to discover an accepted, authorized nomenclature for DNA sequence numbering. The Web page for the nomenclature committee of the International Union of Biochemistry and Molecular Biology provides no guidance. The world's largest genetic sequence data bases, NCBI/GenBank, European Molecular Biology Laboratory-Nucleotide Sequence Database, and the DNA Data Bank of Japan, number sequences as entered, beginning with 1, irrespective of function or structure. The Rat Genome Database refers to these databases. COMPEL, a database of composite regulatory elements affecting gene transcription in eukaryotes allows description of the alternative reference origins for numbering sequences, but does not contain entries for either rat insulin-like growth factor binding protein-1 (IGFBP-1) or pyruvate kinase.

Further, in scientific publications dealing with a single gene, sequence numbers are often referenced to either the transcription initiation site, or the translation initiation site. However, publications dealing with the same or similar

sequences are inconsistent with respect to which reference site they utilize. For example, Unterman et al. (of record) number the published sequence of the rat IGFBP-1 promoter beginning with the translation start site. In a later publication, these same authors number the same sequence beginning with the transcription start site (Goswami et al. - of record). Similarly, Cognet et al. (of record) initiate promoter sequence numbering for the rat liver pyruvate kinase (L-PK) promoter from the transcription start site, while Inoue et al. (of record) utilize the translation start site.

Across publications, the numbering of similar sequence bases is inaccurate. For example, in Yamada et al. (of record), the L-PK promoter base designated as -126 is identified as -124 in Cognet et al. Even within a single publication, sequence numbering is inaccurate. In Goswami et al. base number -110 in Figure 3, corresponds to base number -109 in Figure 7. In Unterman et al. (of record) the base indicated as -109 in Figure 4, is referred to as -116 in Material and Methods.

Further, accounting for differences with respect to which start site is chosen and reported, sequences falling within numeric ranges fail to match across publications. The rat L-PK promoter sequences beginning with -1 in Inoue et al. do not match the promoter bases presented in Cognet et al. Similarly, the bases designated by the numbers -149- -146 of L-II in Table 1 of Yamada et al. are without correlation in the sequence offered by Cognet et al.

Moreover, it is submitted that the numbers presented in the Thulé and Liu presentation slides do not correlate with the claimed sequences. For instance, the numbers for the IGFBP-1 sequences indicate that the $(GIRE)_3$BP-1 promoter includes bases -111 to 96+ of IGFBP-1. However, the sequence in SEQ ID NO: 5 of the claimed invention, encompasses bases best indicated by base numbers -114 to +105 of the IGFBP-1 promoter with respect to the transcription start site. Likewise, the L-PK promoter sequence numbers presented, -173 to -125, also do not correlate. SEQ ID NO: 5 encompasses three head-to-tail repeats of bases best indicated by base numbers -173 to -123, respective to the transcription start site.

In summary, there exists no standard, accepted numbering system for DNA sequence bases or base pairs with respect to function or replication. The largest most commonly used DNA sequence data bases number entered sequences from 1 onward. All other numberings of DNA sequences must be coupled with a referenced initiation to be useful. Such a reference was not provided in the slide presentations. Published literature referring to both the rat L-PK and rat IGFBP-1 promoters were not uniform in their use of an internal reference, even within authors. Moreover, base numbers in published sequences of rat L-PK and rat IGFBP-1 promoters were inconsistent both within single publications and across publications. Further, published literature is not concordant with respect to promoter sequences, particularly of the rat L-PK promoter. Additionally, the numbers presented in the slides do not correlate with SEQ ID NO: 5. Consequently, the

numbers provided in the presentations do not, and could not, accurately and reliably disclose the claimed sequence of SEQ ID NO: 5.

In view of the above, it is respectfully submitted that even if, *arguendo*, the Thulé and Liu presentations could be relied upon, they do not disclose nor would enable one of ordinary skill in the art to reconstruct the claimed sequences.

In the Office Action of March 20, 2007, the Examiner stated the following:

> Thulé (Diabetes) is an abstract from a presentation that the inventor gave more than one year before the effective filing date of the instant application. The abstract teaches an adenoviral vector which is described as comprising all of the claimed elements, and which also named Ad/(GIRE)$_3$BP-1 2xfur. Since the Ad/(GIRE)$_3$BP-1 2xfur vector taught by the Thulé (Diabetes) abstract appears to be the same vector described in the specification, it must, by necessity meet all of the limitations of the claims. Furthermore, in the presentation given by the Inventor at the ADA 59th Annual Meeting June 1999, which is the presentation associated with the Thulé (Diabetes) abstract, the slides (e.g., see slides 2 and 3) clearly describe the elements used to construct the Ad/(GIRE)$_3$BP-1 2xfur vector. Specifically, the slides indicate the exact nucleotides of the rL-PK (nucleotides -125 to -173) and rIGFBP-1 (nucleotides -111 to +96) promoted elements used to construct the vector. (Emphasis added).

Page 4, 1st ¶.

It is clear from the above[5] that the Examiner is not merely relying on the presentation to allegedly explain the meaning of the term "adenoviral vector," which

[5] It is noted that similar reasoning was advanced on page 6, 1st ¶ (full) and page 8, 2nd ¶ (full) in support of other anticipation rejections.

is named "Ad/$(GIRE)_3$BP-1 2xfur," but has expanded its meaning by linking it to what is disclosed in the specification. In doing so, the Examiner has used the Applicant's own disclosure against him in rejecting the claims. It is well settled law that an Applicant's own teachings cannot be used to support of a rejection. *In re Kuehl*, 475 F. 2d 658,177 USPQ 250 (CCP A1973). In this regard, it is noted again that neither the Thulé Abstracts nor the Thulé and Liu presentations disclose the specific sequences recited in Claim 9. The presentations merely disclose numbering of portions of the sequences set forth in Claim 9.

In order to fill the gap of Claim 9 sequences, in the Thulé Abstracts and the presentations, the Examiner presented Vaulont et al. and Goswami et al. publications.

It is respectfully submitted that both Vaulont et al. and Goswami et al. disclose not specifically what was disclosed in the presentations or recited in Claim 9, but longer sequences that allegedly may overlap with the numbering of the nucleotides disclosed in the presentations. In other words, neither Vaulont et al. nor Goswami et al. disclose the sequences of Claim 9. In addition, as noted above, the numbers presented in the presentations are ambiguous and non-enabling to one skilled in the art. The numbers referring to the bases or base pairs appearing in genetic sequence data are only interpretable when combined with the referenced origin. An origin or reference start of numbering was not provided in the presentations. The sequence numbers provided are, therefore, non-specific and ambiguous.

As also noted above, in various scientific publications dealing with a single gene, sequence numbers are often referenced to either the translation initiation site, or the transcription initiation site. In this regard, Applicant notes the Examiner's citation of Genes & Genomes (Sanger and Burg, 1991), which teaches sequence numbering relative to the transcription start site. However, Applicant asserts that the numbering of sequences relative to the transcription start site, as taught by Genes & Genomes, is by no means a gold standard. As a result, reliance on the Thulé and Liu presentations and Vaulont et al. and Goswami et al. publications, to explain the meaning of the term "Ad/$(GIRE)_3$BP-1 2xfur or any other sequence element, "as the Examiner asserts, could not, and would not shed light on what the individual elements of that term would have meant to those skilled in art vis-à-vis the claimed sequences.

In view of the above, it is respectfully submitted that the Examiner's reliance on multiple references does not comport with the modest flexibility in the "anticipation" rule.

d. Examiner's Reliance on Multiple References for Inherency of the Claimed Nucleotide Sequences is Improper

In support of his anticipation rejections over Thulé and Liu presentations and Vaulont et al. and Goswami et al. publications, the Examiner stated that the nucleotide sequences not disclosed in the primary reference, the Thulé et al.

Abstracts, are inherent. See Final Rejection dated December 12, 2007, Page 6, 1st ¶ (full).

As noted by the Federal Circuit in *Continental Can*, other references may be used in support of anticipation "where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges." 948 F.2d at 1269.

Further, the gap or silence about the asserted inherent characteristic - the specific nucleotide sequences of Claim 9 - may be filled by extrinsic evidence, which-

> must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can, supra, at 1268.

Accordingly, inherency allows, in very limited circumstances, an invention to be anticipated by prior art that is lacking minor, well-known features in the claimed invention. Donner, Irah H., *Patent Prosecution: Law, Practice, and Procedure*, 5th Ed., Vol. 1, p.1235 (2007).

The present invention is directed to specific nucleotide sequences for an adenoviral chimeric vector-construct prepared in lab. More specifically, one or more glucose-responsive fragments from the rat L-pyruvate kinase gene are inserted into the insulin-like growth factor binding protein-1 basal promoter. The resultant chimeric sequence is then coupled with a human insulin expression sequence. The

final transgene is incorporated into an adenoviral vector. The inventor confirmed the ability of the vector to induce insulin production and to respond to glucose *in vivo*. In other words, the inventive insulin transgene was expressed and functional (see Figure 15B and paragraph [0069] of the application).

By nature, and is well-known, the field of biotechnology is unpredictable. As is also well-known, expression and/or functionality of a gene can be entirely affected by, for example, changing, deleting, or skipping, even one base or nucleotide. In other words, it is critical and necessary that the exact sequence be available for the genetic transcription/expression machinery to achieve the intended function or expression. It goes without saying, therefore, that the knowledge of the precise nucleotide numbering is vital.

Although various nomenclature for sequence numbering presently exist in the art, such as one noted by the Examiner on page 8 of the Final Rejection dated December 13, 2007, there is completely absent a single, widely-accepted, methodology for such. Accordingly, a particular sequence numbering cannot be relied upon to a certainty needed in genetic engineering or biotechnology to duplicate with the confidence that the law requires. As the Federal Court stated-

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. (Emphasis in original).

Continental Can, *supra,* at 1269.

In other words, what is missing must necessarily result from the prior art reference.

In view of the non-specific and ambiguous nature of the nucleotide numbering shown in the Thulé and Liu presentation slides and the lack of a single, widely-accepted gold standard nomenclature for DNA sequence numbering, it is respectfully submitted that one of ordinary skill in the art, cannot and would not be able necessarily to duplicate the sequences recited in Claim 9.

In the "Response to Arguments" section, on page 8 of the Final Rejection dated December 12, 2007, the Examiner stated the following:

> With respect to Applicant's argument that the disclosed sequences do not exactly correlate with the claimed sequences, it is noted that the sequences at issue are expression regulatory elements that were each known in the prior art (i.e., they were not novel). That is, the nucleotide sequence which confers the function were known. The presentations given by the Applicant disclosed the arrangement of the known elements into particular configurations which conferred a specific function. Applicant's abstract, relied on as prior art, teaches a construct identified as the same construct of the instant claims and teaches the construct has all of the same functional characteristics as the claimed construct. The information that Applicant disclosed in the presentations further described the construct and based on the information that was available in the prior art, gave enough information to one of ordinary skill in the art (such as one attending the presentation) would be able to make the construct disclosed in the abstract, which would essentially be the same as the claimed construct as it would not only have the same function (as is indicated in the abstract) but also have the elements (sequences) critical for the function. (Emphasis added).

From the above, it appears that the Examiner believes that by merely knowing individual promoter sequences, one can simply mechanically join them

together to obtain the desired functionality with acceptable predictability.

Applicant respectfully disagrees.

Both the unpredictability and the level of expertise needed in biotechnical arts are high. Consequently, one skilled in the art would not undertake duplicating the claimed construct, absent the present invention and the supporting experimental data. The inventor herein not only created a novel, expressing insulin transgene, he demonstrated its functionality and efficacy in modulating hyperglycemia, while avoiding lethal hypoglycemia, even during a 24 hour fast (see, for example, paragraphs [0017-0019], [0064-0079] and [0084-0087], and Figures 15A-15B, 23 and 26A-26B of the application). To state, as has the Examiner, that the Thulé Abstracts, the Thulé and Liu presentations and the general disclosures of promoter elements in Vaulont and Goswami publications, would enable one of ordinary skill in art, but without the supporting experimental data, is tantamount to hindsight reconstruction which is prohibited by law. This is indicated by the Examiner's finding that the name/identification of the construct disclosed in the Thulé Abstracts is the same as that disclosed in the specification.

In order to prevent the use of hindsight, the Federal Circuit has stated:

> In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. (Citation omitted).

Ruiz v. A.B. Chance Co., 234 F.3d 654, 57 USPQ2d 1161 (Fed. Cir. 2000).

In other words, the Applicant's disclosure may not be used "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit". *Green Processing Corp. v. American Maize-Products*, 840 F.2d 902, 907 (Fed. Cir. 1988). In this regard, the Federal Circuit has stated:

> [I]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. . . This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." (Emphasis added).

In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992).

In view of the above, it is respectfully submitted that the sequences of Claim 9, are not described in Thulé Abstracts and, due to the unpredictable nature of the art and lack of a single, widely-accepted standard for sequence nomenclature, could not be recognized by one of ordinary skill in the art.

Claims 1-8 and 10-15

Claim 1

It is further respectfully submitted that the subject matter of Claim 1, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

Claim 2

It is further respectfully submitted that the subject matter of Claim 2, which further limits Claim 1, is separately and independently patentable for the reasons discussed above in connection with Claims 1 and 9, and its lack thereof in the prior art of record.

Claim 3

It is further respectfully submitted that the subject matter of Claim 3, which further limits Claim 2, is separately and independently patentable for the reasons discussed above in connection with Claims 1-2 and 9, and its lack thereof in the prior art of record.

Claim 4

It is further respectfully submitted that the subject matter of Claim 4, which further limits Claim 2, is separately and independently patentable for the reasons discussed above in connection with Claims 1-2 and 9, and its lack thereof in the prior art of record.

Claim 5

Claim 5 recites that the positions of HNF-4 binding site and glucose responsive site are reversed from a native orientation. It is respectfully submitted that none of the cited references teaches this feature in such explicit detail as to be recognized by one skilled in the art, absent the claimed invention. Therefore, even

if, *arguendo*, the native orientation is known, the claimed reversed order is not anticipated. See *Lindemann, supra*.

It is further respectfully submitted that the subject matter of Claim 5, which further limits Claim 2, is separately and independently patentable for the reasons discussed above in connection with Claims 1-2 and 9, and its lack thereof in the prior art of record.

Claim 6

It is further respectfully submitted that the subject matter of Claim 6, which further limits Claim 1, is separately and independently patentable for the reasons discussed above in connection with Claims 1 and 9, and its lack thereof in the prior art of record.

Claim 7

It is further respectfully submitted that the subject matter of Claim 7, which further limits Claim 1, is separately and independently patentable for the reasons discussed above in connection with Claims 1 and 9, and its lack thereof in the prior art of record.

Claim 8

It is further respectfully submitted that the subject matter of Claim 8, which further limits Claim 1, is separately and independently patentable for the reasons discussed above in connection with Claims 1 and 9, and its lack thereof in the prior art of record.

Claim 10

It is further respectfully submitted that the subject matter of Claim 10, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

Claim 11

It is further respectfully submitted that the subject matter of Claim 11, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

Claim 12

It is further respectfully submitted that the subject matter of Claim 12, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

Claim 13

It is further respectfully submitted that the subject matter of Claim 13, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

Claim 14

It is further respectfully submitted that the subject matter of Claim 14, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

Claim 15

It is further respectfully submitted that the subject matter of Claim 15, which further limits Claim 9, is separately and independently patentable for the reasons discussed above in connection with Claim 9, and its lack thereof in the prior art of record.

VIII. CONCLUSION

For the foregoing reasons, Appellant's presently claimed invention contains patentable subject matter that may not be properly rejected under 35 U.S.C. §102(b) Thulé et al. Abstracts (Diabetes, May 1999, supplement), (Abstract from the Meeting of June 9-13, 1999), and (Abstract from the Meeting of June 1998); Thulé and Liu presentation at the ADA 59th Annual Meeting, June 1999 (Reference #3 in the IDS filed on March 14, 2006), Thulé and Liu presentation at the American Society of Gene Therapy, 2nd Annual Meeting, June 1999 (Reference #4 in the IDS filed on March 14, 2006), and Thulé and Liu presentation at the ADA 58th Annual Meeting, June 1998 (Reference #2 in the IDS filed on March 14, 2006); and

Vaulont et al. (*J. Mol. Biol.* 1989, Vol. 209, pp. 205-219) and Goswami et al. (*Endocrinology*, 1994, Vol. 134, pp. 736-743) publications. Accordingly, this Honorable Board is respectfully requested to reverse the rejections of Claims 1-15.

Respectfully submitted,

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August 14, 2008
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/972,916	Confirmation No.: 4645
Applicant	:	Peter M. THULÉ, M.D.	
Filed	:	October 10, 2001	
Title	:	GLUCOSE SENSITIVE REGULATOR OF INSULIN TRANSCRIPTION	
Group Art Unit	:	1635	
Examiner	:	ANGELL, Jon E.	
Atty. Docket No.	:	US 1292/01(VA)	
Date	:	August 14, 2008	

CLAIMS APPENDIX

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Claim 1. The insulin regulator construct of Claim 9, wherein the nucleotide sequence comprises:

a) a glucose response element (GIRE) of a liver-pyruvate (L-PK) gene promoter; and

b) an insulin-sensitive element of an insulin-like growth factor binding protein-1 (IGFBP-1) basal promoter.

Claim 2. The insulin regulator construct of Claim 1, wherein:

said glucose response element comprises a hepatic nuclear factor-4 (HNF-4) binding site and a glucose responsive site.

Claim 3. The insulin regulator construct of Claim 2, further comprising:

a plurality of said glucose response elements.

Claim 4. The insulin regulator construct of Claim 2, wherein:

the sequence of said HNF-4 binding site and said glucose responsive site is in a native orientation.

Claim 5. The insulin regulator construct of Claim 2, wherein:

the sequence of said HNF-4 binding site and said glucose responsive site is reversed from a native orientation.

Claim 6. The insulin regulator construct of Claim 1, wherein:

said glucose response element is inserted upstream of said insulin-sensitive element in an insulin-like growth factor binding protein-1 (IGFBP-1) basal promoter.

Claim 7. The insulin regulator construct of Claim 1, wherein:

said glucose response element comprises a nucleotide sequence set forth in SEQ ID NO.: 1.

Claim 8. The insulin regulator construct of Claim 1, wherein:

said insulin-sensitive element comprises a nucleotide sequence set forth in SEQ ID NO.: 2.

Claim 9. An insulin regulator construct, comprising:

a) a nucleotide sequence set forth in one of SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, and SEQ ID NO.: 6; and

b) a sequence encoding insulin or proinsulin operably linked to the promoter element of said construct.

Claim 10. The insulin regulator construct of Claim 9, which is not stimulated by exposure to lactate or fructose.

Claim 11. The insulin regulator construct of Claim 9, which is stimulated by exposure to glucose and inhibited by exposure to insulin.

Claim 12. A vector comprising the construct of Claim 9.

Claim 13. An adenoviral vector comprising the construct of Claim 9.

Claim 14. The construct of Claim 9, wherein said construct comprises a transgene.

Claim 15. A pharmaceutical composition comprising the construct of Claim 9 and a pharmaceutically acceptable carrier or diluent.

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EVIDENCE APPENDIX

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None.

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RELATED PROCEEDINGS APPENDIX

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None.